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Synthesis of new 4-butyl-arylpiperazine-3-(1*H*-indol-3-yl)pyrrolidine-2,5-dione derivatives and evaluation for their 5-HT_{1A} and D_2 receptor affinity and serotonin transporter inhibition

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ABSTRACT

A series of novel 4-butyl-arylpiperazine-3-(1*H*-indol-3-yl)pyrrolidine-2,5-dione derivatives were synthesized and evaluated for their 5-HT_{1A}/D_2 receptor affinity and serotonin reuptake inhibition. The compounds exhibited high affinity for the 5-HT_{1A} receptor, (especially **4d** K_i = 0.4 nM) which depended on the substitution pattern at the phenylpiperazine moiety. From this series screen, compound **4c** emerged with promising mixed receptor profiles for the 5-HT_{1A}/D_2 receptors and the serotonin transporter (K_i = 1.3 nM, 182 nM and 64 nM, respectively).

1. Introduction

Serotonin (5-HT) regulates several physiological processes such as mood, appetite and sleep [1]. Consequently, 5-HT neurotransmission dysfunction is often observed in schizophrenia, depression, anxiety and obsessive–compulsive disorder [2]. One hypothesis explaining the pathophysiology of depression is the "monoamine hypothesis". It states that the functional deficiency of monoamines (5-HT, dopamine (DA) and noradrenaline (NE)) seen in depression results from decreased protein transporter activity and abnormalities in the neurotransmitter function of receptors. A recent work [3] suggests that reversal of this effect and restoration of 5-HT are possible using a multimodal treatment approach which involves targeting many receptors of neurotransmitters at the same time. Of the multiple therapeutics used for the treatment of depression, the selective serotonin reuptake inhibitors (SSRIs) play a prominent role. The therapeutic effect that can be observed after the administration of an SSRI drug is the sum of neurochemical alterations taking place in the brain, including desensitization of 5-HT_{1A} autoreceptors, down-regulation of receptors for neurotransmitters, changes in signal transmission, neurotropism, mobilization and an increase in neurogenesis in the hippocampus [1]. Despite comprehensive research on the development of pharmacotherapies against the disease, current anti-depressants are limited by delayed onset of action, safety and efficacy issues [4]. Thus, there is a need for better treatment strategies. One possible strategy to achieve this goal is combining SSRIs with an agonist/antagonist activity at various serotonin receptors.

The 5-HT_{1A} receptor ligands seem to be particularly promising in the treatment of mental diseases such as depression and schizophrenia [5]. The 5-HT_{1A} receptor belongs to the G protein-coupled receptors and exists as an autoreceptor and a heteroreceptor. Its highest concentration is observed in the limbic system and raphe nuclei of the brain stem, as well as in the cerebral cortex, thalamus, hypothalamus and basal nuclei [4]. The 5-HT_{1A} receptor activation by endogenous 5-HT or local agonist application inhibits both serotonergic and non-serotonergic neurons [6]. The simultaneous administration of SSRI and a 5-HT_{1A} receptor agonist/partial agonist causes a rapid increase in neurotransmission in the serotonergic system, *via* a postsynaptic receptor stimulation. The release of endogenous serotonin is inhibited by a negative feedback loop activated by the stimulation of

Abbreviations: 5-HT, serotonin; SSRI, selective serotonin reuptake inhibitor; SERT, serotonin transporter; DA, dopamine; LCAPs, long-chain arylpiperazines; SAR, structure-activity relationship; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; TLC, thin layer chromatography; PhPs, phenylpiperazines; ilPFC, infralimbic prefrontal cortex

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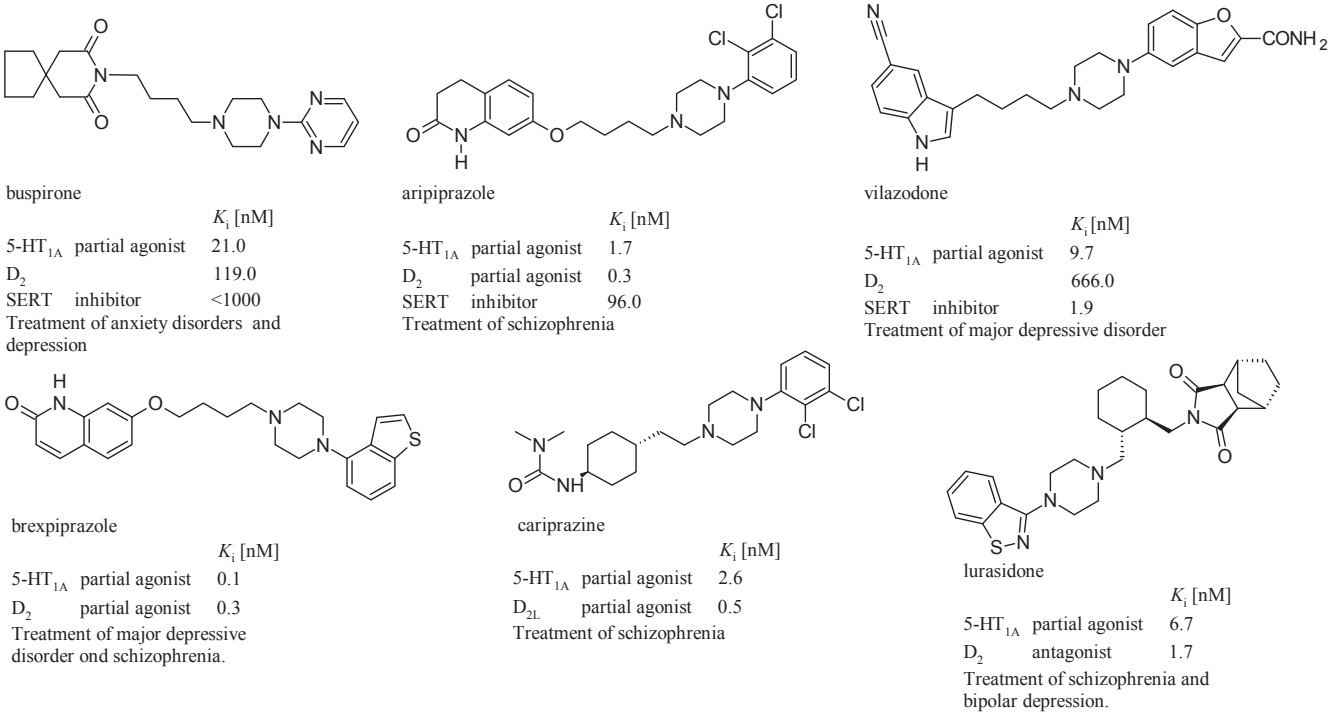


Fig. 1. Chemical structures of representative long-chain arylpiperazines (LCAPs) used as antidepressant and antipsychotics (taken/adapted from [10–13]).

somatodendritic autoreceptors [7]. Recently, the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study revealed that, in patients unresponsive to SSRIs alone, treatment augmentation with buspirone resulted in symptom remission. From a functional perspective, buspirone, a partial 5-HT$_{1A}$ receptor agonist, facilitates the desensitisation of 5-HT$_{1A}$ autoreceptors, which may be a reason for the increased clinical efficiency of SSRIs (Fig. 1) [8]. Recently, a combinatorial approach using serotonin transporter (SERT) inhibition with a 5-HT$_{1A}$ receptor agonism (SSRI/5-HT$_{1A}$ dual-activity) appeared to be a viable therapeutic approach. Two excellent examples of such drugs are vortioxetine and vilazodone [9].

Long-chain arylpiperazines (LCAPs) have established their position as favourable scaffolds for 5-HT$_{1A}$ receptor binding. Buspirone is a prototype medication in this chemical class of compounds (Fig. 1) [14,15]. As a result of the redesign of buspirone, many compounds with affinities for the 5-HT$_{1A}$ receptor have been obtained. For example, Mokrosz *et al.* 1995, reported on a series of 4-(4-succinimidobutyl)piperazine derivatives of buspirone analogues and NAN190, of which the most important compounds were MM199, MM77 and MP359 (Fig. 2) [16–23].

Further LCAP studies identified structural features important for ligand binding with the 5-HT$_{1A}$ receptor, in particular the aryl ring at the N1 atom of the piperazine framework [24]. These studies evaluated the length and flexibility of the alkyl chain at the N4 position. In contrast, the influence of the amide or the imide group is controversial. One study suggests they stabilise the ligand-receptor complex [14], whereas others suggest little or no influence on receptor binding [25,26]. Study data focusing on the binding of LCAPs to 5-HT$_{1A}$ receptors appear equivocal in terms of the significant effects of the variations of the alkyl spacer (i.e. its length and conformational dynamics) on pharmacological profiles of the compounds [27].

Numerous preclinical and clinical studies have indicated that disturbances in central serotonin activity are key factors in depression [5,28]. However, other monoaminergic neurotransmitters like DA have also been implicated. Many symptoms observed in depression (e.g. anhedonia) have been linked with dysfunction of DA metabolism, especially with decreased tonic dopamine neuron firing by activation of the infralimbic prefrontal cortex (ilPFC) [29]. It is accepted that 5-HT receptors indirectly modulate dopamine release from neurons [30]. Moreover, drugs that simultaneously target D$_2$ and 5-HT$_{1A}$ receptors may be advantageous for the pharmacotherapy of schizophrenia (Fig. 1) [31]. Clinical studies have shown that the co-administration of 5-HT$_{1A}$ agonists with typical or atypical neuroleptics may enhance the antipsychotic effects of these latter drugs, especially in terms of reducing cognitive deficits [32,33]. Despite numerous compounds with various chemical scaffolds that have been synthesized as potential antidepressant and antipsychotics, LCAPs remain one of the most versatile drug templates with high affinities for 5-HT$_{1A}$ and D$_2$ receptors [34,35].

As depression and schizophrenia are complex neurological disorders with many different symptoms, introducing multi-target drugs with polypharmacological profiles has become a widely used therapeutic approach [36]. Nowadays, LCAPs with affinities for 5-HT$_{1A}$/D$_2$ receptors and/or serotonin reuptake inhibition are used as medication and include; buspirone (anxiolytic), vilazodone (antidepressant),

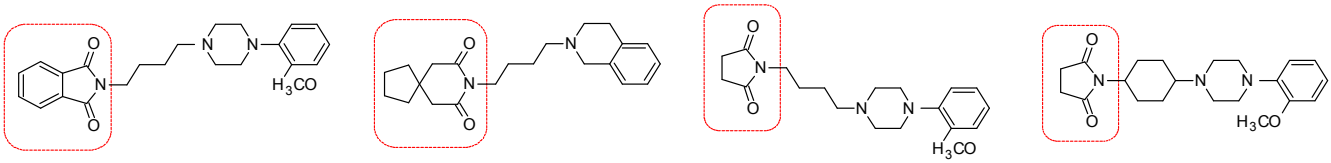


Fig. 2. LCAP examples with imide moieties in the terminal part. All of them show high affinity for the 5-HT$_{1A}$ receptor [11].

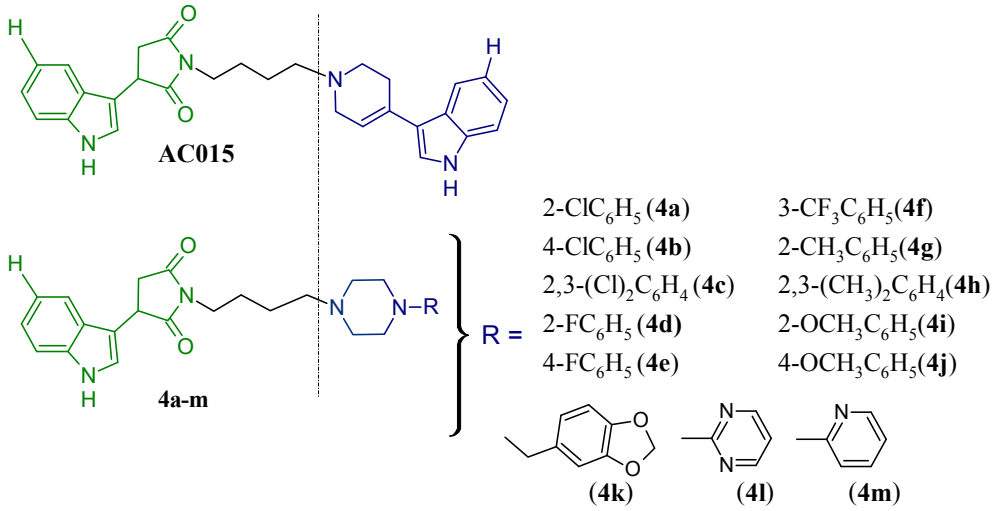


Fig. 3. Structural features of previously synthesized reference compound **AC015** and newly synthesized LCAPs (**4a–m**).

cariprazine, aripiprazole, lurasidone and brexpiprazole (neuroleptics) (Fig. 1). Developing new multi-target antipsychotics and antidepressants, which act on dopaminergic and serotoninergic receptors with balanced receptor activities, has been our research goal.

In our previous paper, we described the synthesis and biological evaluation of a number of pyrrolidine-2,5-dione derivatives, with good double binding to the 5-HT_{1A} receptor and SERT [37]. In the current study, we focused on increasing binding affinity for the 5-HT_{1A} receptor, while maintaining high affinity for SERT (Fig. 3) in a group of test compounds.

We have selected 1-{4-[4-(1*H*-indol-3-yl)-3,6-dihydro-2*H*-pyridin-1-yl]butyl}-3-(1*H*-indol-3-yl)pyrrolidine-2,5-dione (**AC015**) as a reference compound due to its promising double affinity for SERT and the 5-HT_{1A} receptor (5-HT_{1A} K_i = 12.5 nM; SERT K_i = 11.3 nM) (Fig. 3) [37]. Here, we conducted a new exploratory study with the replacement of the 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole moiety with arylpiperazine residues and synthesized derivatives (**4a–m**). As a continuation of our study on pyrrolidine-2,5-dione derivatives, we now report on the design and synthesis of a new series of **AC015** analogues and 4-butyl-arylpiperazine-3-(1*H*-indol-3-yl)pyrrolidine-2,5-dione derivatives. Since clinical and pre-clinical studies indicate that 5-HT_{1A} and D_2 receptor ligands simultaneously exhibit serotonin reuptake inhibition, and that this combination may have a potential for treating mood disorders, we evaluated the newly designed compounds for 5-HT_{1A}/D_2 receptor affinity and serotonin reuptake inhibition in radioligand binding assays.

2. Results and discussion

2.1. Chemistry

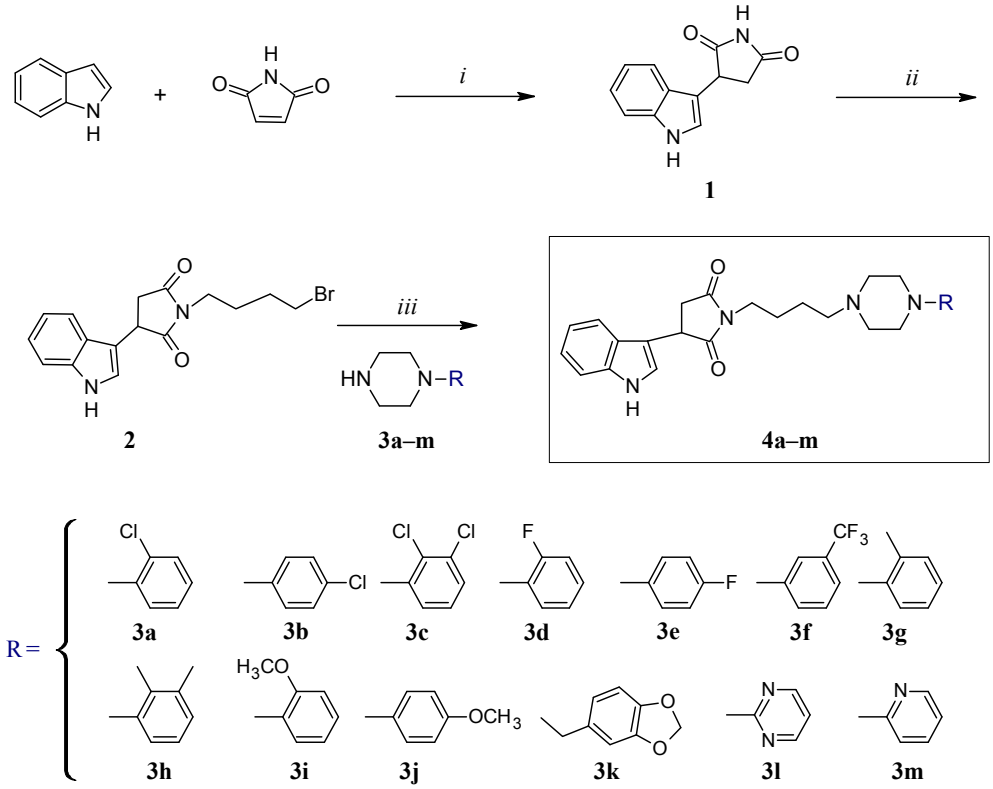
The target compounds **4a–m** were obtained *via* a three-step synthesis (Scheme 1). First, 3-(1*H*-indol-3-yl)pyrrolidine-2,5-dione (**1**) and 1-(4-bromobutyl)-3-(1*H*-indol-3-yl)pyrrolidine-2,5-dione (**2**) were synthesized according to a previously described procedure (for more information see supplementary materials and [37–40]). Macor *et al.* [40], first described the synthesis mechanism of 3-(1*H*-indol-3-yl) pyrrolidine-2,5-dione in acetic acid. They noted that a one-step reaction of maleimide with 1*H*-indole to form a C—C bond is only possible when it is carried out in an acid solvent. They reported that maleimide is activated by the acid which increases its acceptor reactivity in the Michael addition. According to Henon *et al.* and Bergman *et al.* [38,39] in some cases, the side product 5,13-dihydro-6*H*-indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazole-6,8(7*H*)-dione was isolated along with compound **1**. Future study showed that, in order to avoid this side product, it is important to carry out the reaction at the boiling point of the solvent (117–118 °C for glacial acetic acid), and the molar ratio between maleimide and indole should be 3:1. The alkylation agent (dibromobutane) was used in a large excess (9 mol) in the *N*-alkylation step in order to avoid the reaction of disubstitution leading to *N,N*-(butane-1,4-diyl)bisimides. The final compounds **4a–m** were obtained by *N*-alkylation of the intermediate **2** with the appropriate arylpiperazines **3a–m** (Scheme 1) [37].

2.2. In vitro receptor affinity and structure-activity relationship (SAR) determination

The synthesized compounds were tested for their *in vitro* affinity for the 5-HT_{1A} and D_2 receptor and inhibition of SERT using a radioligand binding assay, according to procedures described in the experimental section. The results are presented in Table 1.

The series **4a–m** was designed to achieve compounds with high affinities for 5-HT_{1A}, with additional SERT and/or D_2 receptor activities. The chemical structure of our compounds meets the criteria of the classical pharmacophore for monoaminergic receptor ligands consisting of the protonated amine anchored by Asp3.32 (for review see [41]) and specific hydrophobic recognition involving aromatic interaction (CH–π or π–π) with the Phe6.51/Phe6.52/Trp6.48 aromatic cluster. Additionally, the terminal fragment connected with the basic centre *via* the alkylene linker forms the aromatic and H-bond interactions and stabilizes ligand binding in the second transmembrane pocket between TMHs 7–3 (involving specific amino acids characteristic for serotonin and dopamine receptors) [41]. Our previous docking study [37] of the reference compound **AC015** to the 5-HT_{1A} binding site revealed that the succinimide ring (specifically, the carbonyl oxygen atom) forms a hydrogen bond with Thr196 (2.18 Å) and the position of **AC015** inside the receptor binding pocket is further stabilized by π–π interactions between Phe112 and the indole ring [37]. Further, the docking study of **AC015** to the SERT binding pocket showed formation of a hydrogen bond between the Arg104 residue and the carbonyl oxygen atom of the ligand (2.25 Å). As shown in Table 1, all compounds displayed high affinities for 5-HT_{1A}, with K_i values ranging from 0.4 to 44.0 nM. Moreover, most of the compounds exhibited dual 5-HT_{1A}/SERT activities, in particular compound **4b** (5-HT_{1A} K_i = 25 nM, SERT K_i = 26 nM). These results proved that the chemical structure of the investigated compounds was well justified.

A previous report in the field [42] demonstrated significant interactions between halogen substituents in the phenylpiperazine ring and the binding site of the 5-HT_{1A} receptor, and this modification therefore attracted our attention in this study. More specifically, the role of the halogens has been recently assigned to stabilise ligand–receptor



Scheme 1. The synthesis pathways leading to the arylpiperazine derivatives **4a–m**. Reagents and conditions: (*i*) CH_3COOH (*ii*) $BrCH_2(CH_2)_2CH_2Br$, K_2CO_3, acetone (*iii*) K_2CO_3, $KI_{(cat.)}$, CH_3CN.

complexes *via* the formation of specific halogen bonds [43]. The binding data revealed that compounds having chlorine and fluorine atoms attached to the phenyl displayed similar, high affinities for the 5-HT_{1A} receptor. The most potent were the *ortho*-substituted phenylpiperazines (PhPs), especially the 2-F-PhP derivative **4d** (5-HT_{1A} K_i = 0.4 nM). The introduction of substituents in the *para* position reduced the binding affinity for 5-HT_{1A} receptors. When we compared pairs of *para*- and *ortho*-derivatives, the *ortho* analogues displayed remarkably higher affinities for the 5-HT_{1A} receptor: chloro derivatives **4a** (K_i = 1.6) versus **4b** (K_i = 25.0); fluoro derivatives **4d** (K_i = 0.4) versus **4e** (K_i = 42.0) and methoxy derivatives **4i** (K_i = 1.4) versus **4j** (K_i = 44.0). This observation is in agreement with the previously published data that substituents in *para*-position caused unfavorable steric interactions with the 5-HT_{1A} receptor binding site [17,44,45]. Partyka *et al.*, described an *in silico* experimental study for azinesulfonamides of LCAP derivatives indicating a perturbation of ligand–receptor complex stability (a lack of interaction with Asp3.32 in 5-HT_{1A} binding pocket), in both 4-F-PhP and 4-Cl-PhP derivatives [42]. This may explain the observed decrease of affinity of the investigated *para* substituted compounds.

Interestingly, the *para*-derivatives showed a slightly increased inhibition of SERT, which resulted in compounds with double binding to 5-HT_{1A}/SERT – **4b** (5-HT_{1A} K_i = 25 nM, SERT K_i = 26 nM) and **4j** (5-HT_{1A} K_i = 44 nM, SERT K_i = 30 nM). In contrast, compounds **4i**, **4l** and **4m,** with a 2-methoxyphenyl, pyrimidine or pyridine substituent, respectively, exhibited high 5-HT_{1A} receptor potency, but negligible inhibition of SERT. Replacement of the chlorine atom with fluorine was not preferred for the interaction with SERT; **4a**: (SERT) K_i = 43 nM versus **4d**: (SERT) K_i = 128 nM and **4b**: (SERT) K_i = 26 nM versus **4e**: (SERT) K_i = 102 nM. In summary, substitution at the *ortho*-position of the phenylpiperazine moiety was beneficial for 5-HT_{1A} binding, the *para*-position increased the affinity for SERT and optimal double binding to 5-HT_{1A} /SERT was observed for compound **4b** (4-Cl-PhP derivative).

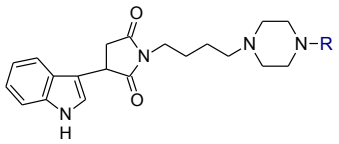
It is worth noting that in this series, compound **4c**, a 2,3-diCl-PhP derivative, was classified as a 5-HT_{1A}/D_2/SERT multi-receptor ligand, with high affinity for all of these receptors (K_i = 1.6 nM, 64 nM and 183 nM, respectively). The analogue with a methoxy group at the *ortho*-position displayed affinity for the D_2 receptor (**4i** K_i = 258 nM), which was in agreement with the literature data [25,46]. The *ortho*-methoxy function is known to be important for constraining the conformation by its ability to form one additional H-bond in the D_2R binding pocket [47]. The *para*-substituted PhPs (compounds **4b**, **4e**, **4j**) were significantly less active in D_2 receptor binding assays than their *ortho*-counterparts. According to the previous study [47], substituents in position 2 and 3 of phenylpiperazine are well tolerated, especially electron donor groups such as *methoxy*. On the other hand, regardless of their size, the 4-substituents are not beneficial for D_2R binding [48]. Šukalović *et al.*, explain this as a result of an unfavorable steric interaction of *para* substituents with Phe178, Tyr216 and Trp182 in the receptor binding pocket. Therefore, the formation of a salt bridge between Asp86 and the protonated nitrogen of the piperazine ring, which is crucial for L–R complex stability, is hindered [47].

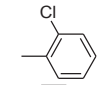
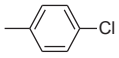
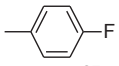
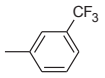
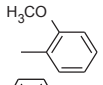
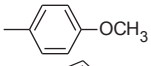
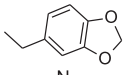
3. Conclusions

In this study, a series of new 4-butyl-arylpiperazine-3-(1*H*-indol-3-yl)pyrrolidine-2,5-dione derivatives (**4a–m)** were synthesized and evaluated as 5-HT_{1A} ligands, with additional serotonin reuptake inhibition and/or D_2 receptor activity. All tested compounds displayed high affinities for 5-HT_{1A}, with K_i values ranging from 0.4 to 44 nM. SAR studies revealed that the affinities of the series compounds for 5-HT_{1A}, SERT and D_2 receptors were highly dependent on substitution patterns of the phenylpiperazine moiety. Moreover, compounds **4a**, **4b**, **4j** and **4k** appeared to be ideal starting points for SSRI/5-HT_{1A} dual-activity agents.

Finally, we identified compound **4c**, a potent, mixed 5-HT_{1A}/D_2/SERT receptor ligand. This compound appears promising in light of the

Table 1
5-HT_{1A}, SERT and D_2 receptor binding affinities of arylpiperazine derivatives **4a–m**.



Compound	R	K_i ± SEM [nM]		D_2
		5-HT_{1A}	SERT	
4a		1.6 ± 0.1	43 ± 3.2	432 ± 27
4b		25 ± 2.3	26 ± 2	> 5000
4c		1.3 ± 0.3	64 ± 7.6	182 ± 18
4d		0.4 ± 0.03	128 ± 18.7	404 ± 42
4e		42 ± 4.5	102 ± 5.3	> 5000
4f		5 ± 0.5	70 ± 6.9	729 ± 67
4g		1.9 ± 0.2	98 ± 8	962 ± 61
4h		1.5 ± 0.1	62 ± 7.8	600 ± 56
4i		1.4 ± 0.1	276 ± 21.3	258 ± 7
4j		44 ± 5.5	30 ± 2.3	Not converged
4k		42 ± 3	28 ± 1.9	Not converged
4l		22.6 ± 1.9	496 ± 35	NT
4m		2.5 ± 0.2	521 ± 42	NT
Serotonin		1.2 ± 0.07	NT	NT
Imipramine		NT	2.0 ± 0.1	NT
Haloperidol		NT	NT	7.5 ± 0.3

NT – not tested.

complexity of CNS disorders and mono-therapy limitations. Overall, these data may merit further *in vitro* studies of compound **4c** as a potentially new multi-target ligand. Such studies will ultimately pave the way in determining its potential *in vivo* antidepressant and/or antipsychotic activity in animal models.

4. Experimental section

4.1. Chemistry

4.1.1. General

All solvents and reagents were purchased from commercial sources and were used without future purification. Melting points were determined on an Electrothermal IA9200 apparatus (Cole-Parmer Ltd., Stone, Staffordshire, UK) with open capillary tubes and were uncorrected. The purity (> 95%) and homogeneity of the compounds were routinely confirmed. Bruker AVANCE III HD 500 MHz (Bruker BioSpin, Rheinstetten, Germany) (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR), Varian INOVA 500 MHz (Varian, Palo Alto, CA, USA) (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR) and Agilent 400-MR DD2 400 MHz (Agilent, USA) spectrometer in $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) were expressed in parts per million (ppm) relative to tetramethylsilane used as the internal reference. The following abbreviations are used to describe peak patterns where appropriate: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), td (triplet of doublets), pt (pseudo triplet), 4d (quartet of doublets), m (multiplet), q (quartet), qu (quintet), * – coupling with fluorine nucleus. Coupling constants (J) are in hertz (Hz).

The High-Resolution Mass Spectrometry (HRMS) was performed using Micromass LCT TOF (Waters Corporation, Milford, MA, USA) mass spectrometer equipped with ESI ionization source, TOF analyser and MCP detector. Samples as 1 mg/L concentration of tested compounds were prepared in methanol. MS detection settings were as follows: source temperature 80 °C, desolvation temperature 150 °C, desolvation gas flow rate 200 L/h, cone gas flow 100 L/h, capillary potential 3.50–5.00 kV, cone potential 26–50 V, extraction cone potential 4–20 V, RF Lens 260–350 V. Nitrogen was used for both nebulizing and drying gas. The data were obtained in a scan mode ranging from 20 to 2000 m/z in time 1.0 s intervals. Data acquisition software was MassLynx V 3.5 (Waters).

Flash column chromatography was carried out on Merck silica gel 60 (230–400 mesh ASTM) using dichloromethane/methanol as the solvent (98:2 *v/v*). Thin layer chromatography was run on Merck silica gel (Kieselgel 60 F_{254}) plates, with mobile phases of dioxane, toluene, ethanol and 25% NH_4OH (6.0:3.2:0.5:0.2, *v/v*) or chloroform, methanol, diethyl ether and NH_4OH (18.0:4.0:3.6:0.4). Compounds were visualized by UV light (254 nm). Room temperature refers to 20–25 °C. Intermediate *1-(4-bromobutyl)-3-(1H-indol-3-yl)pyrrolidine-2,5-dione* (**2**) was obtained following the protocol described in our previous paper (for more information see supplementary materials) [37]. Reagents: maleimide and arylpiperazines derivatives (**3a–m**) were purchased from common commercial suppliers and were utilized without further purification. Atom numbering, ^{1}H NMR and ^{13}C NMR spectra of all synthesized compounds is available in supplementary materials.

4.1.2. General procedure for the synthesis of arylpiperazine derivatives (4a–m)

A mixture of 1-(4-bromobutyl)-3-(1*H*-indol-3-yl)pyrrolidine-2,5-dione (**2**) (1.0 mmol), the appropriate arylpiperazines (**4a–m**) (1.1 mmol), K_2CO_3 (2 mmol), a catalytic amount of KI and 50 mL acetonitrile was stirred and refluxed for 4–5 h. Reaction time was monitored using TLC. After cooling, the mixture was filtered, and the filtrate was evaporated to dryness. The crude residue was purified by flash chromatography using CH_2Cl_2/MeOH (98:2 v/v) as an eluent. Proper fractions were identified by TLC and evaporated to dryness giving analytically pure compounds **4a–m**.

4.1.2.1. 1-(4-(4-(2-chlorophenyl)piperazin-1-yl)butyl)-3-(1H-indol-3-yl) pyrrolidine-2,5-dione (4a). The title compound was isolated as a yellow solid. Yield: 88.0% (0.41 g); m.p. 70–78 °C (melts with decomposition); ESI-HRMS m/z calcd for $C_{26}H_{29}ClN_4O_2H$ $(M+H)^+$ 465.2057, found: 465.2070; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 4.37 (C3H, dd, $^3J_1$ = 9.0, $^3J_2$ = 5.0), 2.83 (C4H(1), dd, ^2J = 18.0, ^3J = 5.0), 3.25 (C4H(2), dd, ^2J = 18.0, ^3J = 9.5), 7.34 (C2′H, d, ^3J = 2.5), 7.41–7.36 (C4′H, C7′H, C3″H, m), 7.01–6.97 (C5′H, m)), 7.12–7.07 (C6′H, m), 3.49 (C1^{x}H$_2$, t, ^3J = 7.0), 1.57 (C2^{x}H$_2$, q, ^3J = 7.0), 1.43 (C3^{x}H$_2$, q, ^3J = 7.0), 2.33 (C4^{x}H$_2$, t, ^3J = 7.0), 2.48 (CaH$_2$, CdH$_2$, bs), 2.94 (CbH$_2$, CcH$_2$, bs), 7.05–7.01 (C4″H, m), 7.31–7.25 (C5″H, m), 7.13 (C6″H, dd, ^3J = 8.0, ^4J = 1.5), 11.05 (N1′H, bs); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 178.4 (C2), 37.6 (C3), 35.9 (C4), 176.7 (C5), 125.8 (C2′), 111.8 (C3′), 118.3

(C3′a), 118.8 (C4′), 121.4 (C5′), 123.5 (C6′), 110.8 (C7′), 136.5 (C7′a), 38.1 ($C1^x$), 25.2 ($C2^x$), 23.6 ($C3^x$), 57.3 ($C4^x$), 52.8 (Ca, Cd), 50.9 (Cb, Cc), 149.1 (C1″), 127.6 (C2″), 130.3 (C3″), 123.8 (C4″), 128.0 (C5″), 120.8 (C6″).

4.1.2.2. 1-(4-(4-(4-chlorophenyl)piperazin-1-yl)butyl)-3-(1H-indol-3-yl) pyrrolidine-2,5-dione ***(4b)***. The title compound was isolated as a yellowish solid. Yield: 82.8% (0.39 g); m.p. 72–75 °C; ESI-HRMS *m/z* calcd for $C_{26}H_{29}ClN_4O_2Na$ $(M+Na)^+$ 487.1877, found: 487.1863; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 4.27–4.22 (C3H, m), 2.90 (C4H(1), dd, ^2J = 18.0, ^3J = 5.0), 3.22 (C4H(2), ^2J = 18.0, ^3J = 9.5), 7.00 (C2′H, dd, ^3J = 2.5, ^4J = 0.5), 7.42 (C4′H, dd, ^3J = 7.5, ^4J = 1.0), 7.14–7.09 (C5′H, m), 7.23–7.16 (C6′H, m), 7.33 (C7′H, dt, ^3J = 8.0, ^4J = 1.0), 3.65 ($C1^xH_2$, t, ^3J = 7.5), 1.74–1.65 ($C2^xH_2$, m), 1.61–1.50 ($C3^xH_2$, m), 2.41 ($C4^xH_2$, t, ^3J = 7.5), 2.55 (CaH_2, CdH_2, t, ^3J = 5.0), 3.12 (CbH_2, CcH_2, t, ^3J = 5.0), 6.81 (C2″H, C6″H, dt, ^3J = 9.0, ^4J = 3.5), 7.19 (C3″H, C5″H, dt, ^3J = 9.0, ^4J = 3.5), 8.51 (N1′H, bs), ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 178.3 (C2), 38.2 (C3), 36.3 (C4), 176.5 (C5), 118.5 (C2′), 111.4 (C3′), 125.7 (C3′a), 122.2 (C4′), 120.1 (C5′), 122.7 (C6′), 111.7 (C7′), 136.6 (C7′a), 38.9 ($C1^x$), 25.8 ($C2^x$), 24.1 ($C3^x$), 57.9 ($C4^x$), 53.0 (Ca, Cd), 49.1 (Cb, Cc), 149.9 (C1″), 117.2 (C2″, C6″), 128.9 (C3″, C5″), 124.4 (C4″).

4.1.2.3. 1-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butyl)-3-(1H-indol-3-yl)pyrrolidine-2,5-dione ***(4c)***. The title compound was isolated as an orange solid. Yield: 79.1% (0.40 g); m.p. 65–75 °C (melts with decomposition); ESI-HRMS *m/z* calcd for $C_{26}H_{29}Cl_2N_4O_2$ $(M+H)^+$ 499.1655, found: 499.1668; ^{1}H NMR (500 MHz, DMSO-d_6) *δ*: 4.36 (C3H, dd, $^3J_1$ = 9.5, $^3J_2$ = 5.0), 2.84 (C4H(1), dd, ^2J = 18.0, ^3J = 5.0), 3.25 (C4H(2), dd, ^2J = 18.0, ^3J = 9.5), 7.34 (C2′H, d, ^3J = 2.0), 7.42–7.36 (C4′H, C7′H, m), 7.02–6.96 (C5′H, m), 7.30–7.26 (C6′H, C5″H, m), 3.49 ($C1^xH_2$, t, ^3J = 7.0), 1.57 ($C2^xH_2$, q, ^3J = 7.0), 1.43 ($C3^xH_2$, q, ^3J = 7.0), 2.33 ($C4^xH_2$, t, ^3J = 7.0), 2.48 (CaH_2, CdH_2, bs), 2.94 (CbH_2, CcH_2, bs), 7.13–7.07 (C4″H, C6″H, m), 11.06 (N1′H, bs, ^3J = 1.5); ^{13}C NMR (125 MHz, DMSO-d_6) *δ*: 178.4 (C2), 37.6 (C3), 35.9 (C4), 176.6 (C5), 118.4 (C2′), 111.8 (C3′), 126.0 (C3′a), 121.4 (C4′), 119.5 (C5′), 123.4 (C6′), 110.8 (C7′), 136.5 (C7′a), 38.1 ($C1^x$), 25.2 ($C2^x$), 23.6 ($C3^x$), 57.2 ($C4^x$), 52.8 (Ca, Cd), 50.9 (Cb, Cc), 151.2 (C1″), 124.3 (C2″), 132.6 (C3″), 125.8 (C4″), 128.4 (C5″), 118.8 (C6″).

4.1.2.4. 1-(4-(4-(2-fluorophenyl)piperazin-1-yl)butyl)-3-(1H-indol-3-yl) pyrrolidine-2,5-dione ***(4d)***. The title compound was isolated as an orange solid. Yield: 93.2% (0.42 g); m.p. 148–149 °C; ESI-HRMS *m/z* calcd for $C_{26}H_{29}FN_4O_2H$ $(M+H)^+$ 449.2353, found: 449.2339; ^{1}H NMR (500 MHz, DMSO-d_6) *δ*: 4.37 (C3H, dd, $^3J_1$ = 9.0, $^3J_2$ = 4.5), 2.83 (C4H(1), dd, ^2J = 18.0, ^3J = 5.0), 3.25 (C4H(2), dd, ^2J = 18.0, ^3J = 9.5), 7.34 (C2′H, d, ^3J = 2.0), 7.44–7.36 (C4′H, C7′H, m), 7.04–6.90 (C5′H, C4″H, C6″H, m), 7.15–7.05 (C6′H, C3″H, C5″H, m), 3.49 ($C1^xH_2$, t, ^3J = 7.0), 1.57 ($C2^xH_2$, q, ^3J = 7.0), 1.43 ($C3^xH_2$, q, ^3J = 7.5), 2.32 ($C4^xH_2$, t, ^3J = 7.0), 2.47 (CaH_2, CdH_2, bs), 2.97 (CbH_2, CcH_2, bs), 11.06 (N1′H, bs); ^{13}C NMR (125 MHz, DMSO-d_6) *δ*: 178.4 (C2), 37.6 (C3), 35.9 (C4), 176.6 (C5), 125.9 (C2′), 111.8 (C3′), 118.4 (C3′a), 118.8 (C4′), 121.4 (C5′), 123.4 (C6′), 110.8 (C7′), 136.5 (C7′a), 38.1 ($C1^x$), 25.2 ($C2^x$), 23.6 ($C3^x$), 57.3 ($C4^x$), 52.7 (Ca, Cd), 50.1 (Cb, Cc), 139.9 (C1″, d*, ^2J = 8.3), 154.9 (C2″, d*, ^1J = 244.3), 115.8 (C3″, d*, ^2J = 20.5), 122.2 (C4″, d*, ^3J = 7.9), 124.8 (C5″, d*, ^4J = 3.3), 119.1 (C6″, d*, ^3J = 3.0).

4.1.2.5. 1-(4-(4-(4-fluorophenyl)piperazin-1-yl)butyl)-3-(1H-indol-3-yl) pyrrolidine-2,5-dione ***(4e)***. The title compound was isolated as a yellow oil at room temperature. Yield: 86.3% (0.39 g); ESI-HRMS *m/z* calcd for $C_{26}H_{29}FN_4O_2H$ $(M+H)^+$ 449.2353, found: 449.2339; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 4.29–4.24 (C3H, m), 2.92 (C4H(1), dd, ^2J = 18.5, ^3J = 5.0), 3.24 (C4H(2), dd, ^2J = 18.5, ^3J = 9.5), 7.05 (C2′H, d, ^3J = 2.5), 7.42 (C4′H, dd, ^3J = 8.0, ^4J = 0.5), 7.14–7.10 (C5′H, m), 7.24–7.19 (C6′H, m), 7.35 (C7′H, dt, ^3J = 8.0, ^4J = ^5J = 1.0), 3.65 ($C1^xH_2$, t, ^3J = 7.0), 1.70 ($C2^xH_2$, q, ^3J = 7.5), 1.56 ($C3^xH_2$, q, ^3J = 7.5), 2.42 ($C4^xH_2$, t, ^3J = 7.5), 2.57 (CaH_2, CdH_2, pt), 3.09 (CbH_2, CcH_2, pt), 6.89–6.83 (C2″H, C6″H, m), 6.98–6.92 (C3″H, C5″H, m), 8.43 (N1′H, bs); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 178.2 (C2), 38.2 (C3), 36.3 (C4), 176.5 (C5), 125.7 (C2′), 111.5 (C3′), 118.5 (C3′a), 120.1 (C4′), 122.2 (C5′), 122.7 (C6′), 111.7 (C7′), 136.6 (C7′a), 38.9 ($C1^x$), 25.8 ($C2^x$), 24.1 ($C3^x$), 57.9 ($C4^x$), 53.2 (Ca, Cd), 50.1 (Cb, Cc), 147.9 (C1″, d*, ^4J = 2.3), 117.8 (C2″, C6″, d*, ^3J = 7.7), 115.5 (C3″, C5″, d*, ^2J = 22.0), 157.1 (C4″, d*, ^1J = 238.9).

4.1.2.6. 3-(1H-indol-3-yl)-1-(4-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)butyl)pyrrolidine-2,5-dione ***(4f)***. The title compound was isolated as an orange solid. Yield: 73.4% (0.37 g); m.p. 63–70 °C; ESI-HRMS *m/z* calcd for $C_{27}H_{29}F_3N_4O_2H$ $(M+H)^+$ 499.2321, found: 499.2311; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 4.32–4.23 (C3H, m), 2.93 (C4H(1), dd, ^2J = 18.5, ^3J = 5.0), 3.25 (C4H(2), dd, ^2J = 18.0, ^3J = 9.5), 7.10–7.01 (C4″H, C6″H, C2′H, C2″H, m), 7.44 (C4′H, dd, ^3J = 8.0, ^4J = 1.0), 7.17–7.00 (C5′H, m), 7.24–7.19 (C6′H, m), 7.36 (C7′H, dt, ^3J = 8.5, ^4J = ^5J = 1.0), 3.66 ($C1^xH_2$, t, ^3J = 7.0), 1.79–1.64 ($C2^xH_2$, m), 1.56 ($C3^xH_2$, q, ^3J = 7.5), 2.42 ($C4^xH_2$, t, ^3J = 7.5), 2.57 (CaH_2, CdH_2, pt), 3.21 (CbH_2, CcH_2, pt), 7.33 (C5″H, t, ^3J = 8.0), 8.35 (N1′H, bs); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 178.2 (C2), 38.2 (C3), 36.3 (C4), 176.5 (C5), 125.7 (C2′), 111.5 (C3′), 118.5 (C3′a), 120.1 (C4′), 122.2 (C5′), 122.7 (C6′), 111.7 (C7′), 136.6 (C7′a), 38.9 ($C1^x$), 25.7 ($C2^x$), 24.1 ($C3^x$), 57.8 ($C4^x$), 53.0 (Ca, Cd), 48.6 (Cb, Cc), 151.3 (C1″), 112.1 (C2″, q*, ^3J = 3.9), 131.4 (C3″, q*, ^2J = 31.7), 115.7 (C4″, q*, ^3J = 3.8), 129.5 (C5″), 118.6 (C6″), 124.3 (C6, q*, ^1J = 272.6).

4.1.2.7. 3-(1H-indol-3-yl)-1-(4-(4-(o-tolyl)piperazin-1-yl)butyl) pyrrolidine-2,5-dione ***(4g)***. The title compound was isolated as a yellow solid. Yield: 80.5% (0.36 g); m.p. 62–76 °C (melts with decomposition); ESI-HRMS *m/z* calcd for $C_{27}H_{32}N_4O_2H$ $(M+H)^+$ 445.2604, found: 445.2615; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.30 (C3H, 4d, $^3J_1$ = 9.5, $^3J_2$ = 4.9, ^4J = 0.9), 3.98–2.88 (C4H(1), CbH_2, CcH_2, m), 3.27 (C4H (2), dd, ^2J = 18.3, ^3J = 9.5), 7.48–7.43 (C4′H, m), 7.25–7.20 (C6′H, m), 7.39 (C7′H, dt, ^3J = 8.2, ^4J = ^5J = 0.9), 3.66 ($C1^xH_2$, t, ^3J = 7.2), 1.76–1.66 ($C2^xH_2$, m), 1.63–1.52 ($C3^xH_2$, m), 2.44 ($C4^xH_2$, t, ^3J = 7.5), 2.58 (CaH_2, CdH_2, bs), 7.19–7.11 (C3″H, C5″H, C2′H, C5′H m), 7.04–7.00 (C6″H, m), 7.04–6.94 (C4″H, m), 2.30 (CH_3, s), 8.17 (N1′H, bs) ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 178.2 (C2), 38.2 (C3), 36.3 (C4), 176.5 (C5), 119.0 (C2′), 111.5 (C3′), 125.7 (C3′a), 122.2 (C4′), 120.1 (C5′), 122.7 (C6′), 111.7 (C7′), 136.6 (C7′a), 38.9 ($C1^x$), 25.8 ($C2^x$), 24.2 ($C3^x$), 58.1 ($C4^x$), 53.7 (Ca, Cd), 51.6 (Cb, Cc), 151.5 (C1″), 132.6 (C2″), 131.0 (C3″), 123.1 (C4″), 126.5 (C5″), 118.5 (C6″), 17.9 (CH_3).

4.1.2.8. 1-(4-(4-(2,3-dimethylphenyl)piperazin-1-yl)butyl)-3-(1H-indol-3-yl)pyrrolidine-2,5-dione ***(4h)***. The title compound was isolated as a yellow solid. Yield: 76.3% (0.35 g); m.p. 70–78 °C; ESI-HRMS *m/z* calcd for $C_{28}H_{34}N_4O_2H$ $(M+H)^+$ 459.2760, found: 459.2754; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 4.28–4.23 (C3H, m), 2.91 (C4H(1), dd, ^2J = 18.5, ^3J = 5.0), 3.22 (C4H(2), dd, ^2J = 18.5, ^3J = 9.5), 7.01 (C2′H, d, ^3J = 2.5), 7.43 (C4′H, dd, ^3J = 8.0, ^4J = 0.5), 7.14–7.09 (C5′H, m), 7.23–7.18 (C6′H, m), 7.34 (C7′H, dt, ^3J = 8.0, ^4J = ^5J = 1.0), 3.66 ($C1^xH_2$, t, ^3J = 7.5), 1.76–1.65 ($C2^xH_2$, m), 1.62–1.52 ($C3^xH_2$, m), 2.44 ($C4^xH_2$, t, ^3J = 7.5), 2.59 (CaH_2, CdH_2, bs), 2.89 (CbH_2, CcH_2, t), 6.90 (C4″H, C6″H, dd), 7.06 (C5″H, t, ^3J = 8.0), 2.26 (2″-CH_3, s), 2.21 (3″-CH_3, s), 8.50 (N1′H, bs); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 178.3 (C2), 38.2 (C3), 36.3 (C4), 176.5 (C5), 118.5 (C2′), 111.4 (C3′), 125.7 (C3′a), 122.2 (C4′), 120.1 (C5′), 122.7 (C6′), 111.7 (C7′), 136.7 (C7′a), 39.0 ($C1^x$), 25.9 ($C2^x$), 24.2($C3^x$), 58.1 ($C4^x$), 53.7 (Ca, Cd), 52.1 (Cb, Cc), 151.5 (C1″), 131.2 (C2″), 137.9 (C3″), 124.9 (C4″), 125.8 (C5″), 116.6 (C6″), 14.0 (2″-CH_3), 20.6 (3″-CH_3).

4.1.2.9. 3-(1H-indol-3-yl)-1-[4-[4-(2-methoxyphenyl)piperazin-1-yl] butyl]pyrrolidine-2,5-dione ***(4i)***. The title compound was isolated as an

orange solid. Yield: 73.0% (0.34 g); m.p. 58–62 °C; ESI-HRMS *m/z* calcd for $C_{27}H_{32}N_4O_3H$ $(M+H)^+$ 461.2553, found: 461.2565; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.28 (C3H, 4d, $^3J_1$ = 9.5, $^3J_2$ = 4.9, ^4J = 0.8), 2.92 (C4H(1), dd, ^2J = 18.4, ^3J = 4.8), 3.24 (C4H(2), dd, ^2J = 18.3, ^3J = 9.5), 7.06 (C2′H, dd, ^3J = 2.6, ^4J = 0.8), 7.47–7.41 (C4′H, m), 7.35 (C7′H, dt, ^3J = 8.2, ^4J = 0.9), 7.15–7.10 (C5′H, m), 7.24–7.18 (C6′H, m), 3.65 ($C1^xH_2$, t, ^3J = 7.1), 1.75–1.66 ($C2^xH_2$, m), 1.64–1.54 ($C3^xH_2$, m), 2.51–2.45 ($C4^xH_2$, m), 2.67 (CaH_2, CdH_2, bs), 3.11 (CbH_2, CcH_2, bs), 7.03–6.97 (C4″H, m), 6.95–6.90 (C3″H, C5″H, m), 6.88–6.84 (C6″H, m) 3.86 (OCH_3, s), 8.51 (N1′H, bs); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 178.3 (C2), 38.1 (C3), 36.3 (C4), 176.5 (C5), 123.0 (C2′), 111.1 (C3′), 125.7 (C3′a), 118.5 (C4′), 120.1 (C5′), 122.2 (C6′), 111.7 (C7′), 136.6 (C7′a), 38.8 ($C1^x$), 25.8 ($C2^x$), 23.8 ($C3^x$), 58.0 ($C4^x$), 53.3 (Ca, Cd), 50.3 (Cb, Cc), 141.1 (C1″), 152.02 (C2″), 118.3 (C3″), 122.6 (C4″), 111.5 (C5″), 121.0 (C6″), 55.3 (OCH_3).

*4.1.2.10. 3-(1H-indol-3-yl)-1-[4-[4-(4-methoxyphenyl)piperazin-1-yl] butyl]pyrrolidine-2,5-dione (**4j**)*. The title compound was isolated as a greenish solid. Yield: 70.3% (0.32 g); m.p. 60–64 °C; ESI-HRMS *m/z* calcd for $C_{27}H_{32}N_4O_3Na$ $(M+Na)^+$ 483.2372, found: 483.2360; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.29 (C3H, 4d, $^3J_1$ = 9.5, $^3J_2$ = 4.9, ^4J = 0.8), 2.94 (C4H(1), dd, ^2J = 18.4, ^3J = 4.9), 3.26 (C4H(2), dd, ^2J = 18.4, ^3J = 9.5), 7.47–7.42 (C4′H, m), 7.16–7.11 (C2′H, C5′H, m), 7.38 (C7′H, dt, ^3J = 8.2, ^4J = 0.9), 7.26–7.19 (C6′H, m), 6.92–6.87 (C2″H, C6″H, m), 6.86–6.81 (C3″H, C5″H, m), 3.65 ($C1^xH_2$, t, ^3J = 7.2), 1.75–1.65 ($C2^xH_2$, m), 1.61–1.51 ($C3^xH_2$, m), 2.46–2.39 ($C4^xH_2$, m), 2.61–2.55 (CaH_2, CdH_2, m), 3.10–3.05 (CbH_2, CcH_2, m), 3.77 (OCH_3, s), 8.21 (N1′H, s); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 178.2 (C2), 38.1 (C3), 36.3 (C4), 176.5 (C5), 125.7 (C2′), 111.7 (C3′), 118.5 (C3′a), 118.2 (C4′), 122.2 (C5′), 122.7 (C6′), 111.5 (C7′), 136.6 (C7′a), 39.9 ($C1^x$), 25.8 ($C2^x$), 24.1 ($C3^x$), 58.0 ($C4^x$), 53.3 (Ca, Ce), 50.5 (Cb, Cd), 145.7 (C1″), 120.1 (C2″, C6″), 114.4 (C3″, C5″), 153.8 (C4″), 55.6 (OCH_3).

*4.1.2.11. 1-(4-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)butyl)-3-(1H-indol-3-yl)pyrrolidine-2,5-dione (**4k**)*. The title compound was isolated as a yellowish solid. Yield: 59.2% (0.29 g); m.p. 75–82 °C (melts with decomposition); ESI-HRMS *m/z* calcd for $C_{28}H_{32}N_4O_4H$ $(M+H)^+$ 489.2502, found: 489.2490; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 4.33–4.28 (C3H, m), 2.93 (C4H(1), dd, ^2J = 18.0, ^3J = 4.5), 3.26 (C4H (2), dd, ^2J = 18.0, ^3J = 9.5), 6.84 (C2′H, d, ^3J = 1.0), 7.45 (C4′H, dd, ^3J = 8.0, ^4J = 1.0), 7.14–7.09 (C5′H, C6″H, m), 7.22–7.17 (C6′H, m), 7.37 (C7′H, dt, ^3J = 8.0, ^4J = ^5J = 1.0), 3.62 ($C1^xH_2$, t, ^3J = 7.0), 1.72–1.63 ($C2^xH_2$, m), 1.62–1.49 ($C3^xH_2$, m), 2.47 ($C4^xH_2$, t, ^3J = 8.0), 2.53 (CaH_2, CbH_2, CcH_2, CdH_2, bs), 3.43 (CeH_2, s), 6.74 (C2″H, C5″H, m), 5.94 ($C7''H_2$, s), 8.44 (N1′H, bs); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 178.3 (C2), 38.1 (C3), 36.3 (C4), 176.5 (C5), 118.6 (C2′), 111.6 (C3′), 125.7 (C3′a), 122.1 (C4′), 120.1 (C5′), 122.7 (C6′), 111.7 (C7′), 136.6 (C7′a), 38.5 ($C1^x$), 25.5 ($C2^x$), 23.3 ($C3^x$), 57.6 ($C4^x$), 52.7 (Ca, Cd), 52.0 (Cb, Cc), 62.4 (Ce), 131.3 (C1″), 107.9 (C2″), 147.7 (C3″), 146.8 (C4″), 109.6 (C5″), 122.4 (C6″), 100.9 (C7″).

*4.1.2.12. 3-(1H-indol-3-yl)-1-[4-[4-(pyrimidin-2-yl)piperazin-1-yl]butyl] pyrrolidine-2,5-dione (**4l**)*. The title compound was isolated as a white solid. Yield: 53.4% (0.23 g); m.p. 56–65 °C (melts with decomposition); ESI-HRMS *m/z* calcd for $C_{24}H_{28}N_6O_2H$ $(M+H)^+$ 433.2346, found: 433.2346; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 4.29 (C3H, 4d, $^3J_1$ = 9.5, $^3J_2$ = 5.0, ^4J = 0.4), 2.94 (C4H(1), dd, ^2J = 18.5, ^3J = 5.0), 3.26 (C4H (2), dd, ^2J = 18.0, ^3J = 9.5), 7.13 (C2′H, dd, ^3J = 2.0, ^4J = 0.5), 7.44 (C4′H, dd, ^3J = 8.0, ^4J = 1.0, ^5J = 0.5), 7.16–7.10 (C5′H, m), 7.25–7.19 (C6′H, m), 7.38 (C7′H, dt, ^3J = 8.0, ^4J = ^5J = 1.0), 3.65 ($C1^xH_2$, t, ^3J = 7.0), 1.76–1.65 ($C2^xH_2$, m), 1.62–1.50 ($C3^xH_2$, m), 2.43 ($C4^xH_2$, t, ^3J = 7.5), 2.49 (CaH_2, [4H], pt), 3.83 (CbH_2, [4H], pt), 8.30 (C4″H, C6″H, d, ^3J = 5.0), 6.48 (C5″H, t, ^3J = 5.0), 8.32 (N1′H, bs); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 178.1 (C2), 38.2 (C3), 36.4 (C4), 176.5 (C5), 122.1 (C2′), 111.7 (C3′), 125.7 (C3′a), 118.6 (C4′), 120.1 (C5′), 122.8 (C6′), 111.7 (C7′), 136.6 (C7′a), 38.8 ($C1^x$), 25.8 ($C2^x$), 24.0 ($C3^x$), 58.0 ($C4^x$), 53.0 (Ca, [2C]), 43.5 (Cb, [2C]), 161.6 (C2″), 157.7 (C4″, C6″), 109.9 (C5″).

*4.1.2.13. 3-(1H-indol-3-yl)-1-[4-[4-(pyridin-2-yl)piperazin-1-yl]butyl] pyrrolidine-2,5-dione (**4m**)*. The title compound was isolated as a white solid. Yield: 49.6% (0.21 g); m.p. 50–56 °C (melts with decomposition); ESI-HRMS *m/z* calcd for $C_{25}H_{29}N_5O_2H$ $(M+H)^+$ 432.2394, found: 432.2394; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 4.29 (C3H, 4d, $^3J_1$ = 9.5, $^3J_2$ = 5.0, ^4J = 1.0), 2.93 (C4H(1), dd, ^2J = 18.0, ^3J = 5.0), 3.26 (C4H (2), dd, ^2J = 18.0, ^3J = 9.5), 7.12 (C2′H, dd, ^3J = 2.5, ^4J = 0.5), 7.44 (C4′H, 4d, ^3J = 8.0, ^4J = 2.0, ^5J = 1.0), 7.17–7.09 (C5′H, m), 7.25–7.19 (C6′H, m), 7.37 (C7′H, dt, ^3J = 8.0, ^4J = ^5J = 1.0), 3.65 ($C1^xH_2$, t, ^3J = 7.0), 1.74–1.67 ($C2^xH_2$, m), 1.62–1.52 ($C3^xH_2$, m), 2.43 ($C4^xH_2$, t, ^3J = 7.0), 2.53 (CaH_2, [4H], pt), 3.53 (CbH_2, [4H], pt), 6.68–6.62 (C3″H, C5″H, m), 7.47 (C4″H, 4d, $^3J_1$ = 8.0, $^3J_2$ = 7.0, ^4J = 2.0), 8.19 (C6″H, 4d, ^3J = 5.0, ^4J = 2.0, ^5J = 0.5), 8.38 (N1′H, bs); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 178.2 (C2), 38.2 (C3), 36.3 (C4), 176.5 (C5), 122.1 (C2′), 111.6 (C3′), 125.7 (C3′a), 118.6 (C4′), 120.1 (C5′), 122.7 (C6′), 111.7 (C7′), 136.7 (C7′a), 38.9 ($C1^x$), 25.8 ($C2^x$), 24.0 ($C3^x$), 58.0 ($C4^x$), 52.9 (Ca, [2C]), 45.1 (Cb,[2C]), 159.5 (C2″), 107.1 (C3″), 137.5 (C4″), 113.3 (C5″), 147.9 (C6″).

4.2. Radioligand binding assay

4.2.1. Preparation of solutions of test and reference compounds

1 mM stock solutions of tested compounds were prepared in DMSO. Serial dilutions of compounds were prepared in 96-well microplate in assay buffers using automated pipetting system epMotion 5070 (Eppendorf). Each compound was tested in 6 concentrations from 10 to 5 to 10–10 M (final concentration).

4.2.2. Serotonin transporter binding assay

Radioligand binding was performed using membranes from HEK-293 cells stably transfected with the human serotonin transporter (PerkinElmer). All assays were carried out in duplicates. 50 μL working solution of the tested compounds, 50 μL [^{3}H]-imipramine (final concentration 2 nM) and 150 μL diluted membranes (9 μg protein per well) prepared in assay buffer (50 mM Tris, pH 7.4, 5 mM KCl, 120 mM NaCl) were transferred to polypropylene 96-well microplate using 96-wells pipetting station Rainin Liquidator (MettlerToledo). Imipramine (10 μM) was used to define nonspecific binding. Microplate was covered with a sealing tape, mixed and incubated for 30 min at 27 °C. The reaction was terminated by rapid filtration through GF/C filter mate presoaked with 0.5% polyethyleneimine for 30 min. Ten rapid washes with 200 μL 50 mM Tris buffer, 154 mM NaCl (4 °C, pH 7.4) were performed using automated harvester system Harvester-96 MACH III FM (Tomtec). The filter mates were dried at 37 °C in forced air fan incubator and then solid scintillator MeltiLex was melted on filter mates at 90 °C for 4 min. Radioactivity was counted in MicroBeta2 scintillation counter (PerkinElmer). Data were fitted to a one-site curve-fitting equation with Prism 6 (GraphPad Software) and K_i values were estimated from the Cheng-Prusoff equation.

4.2.3. 5-HT$_{1A}$ receptor binding assay

Radioligand binding was performed using membranes from CHO-K1 cells stably transfected with the human 5-HT$_{1A}$ receptor (PerkinElmer). All assays were carried out in duplicates. 50 μL working solution of the tested compounds, 50 μL [^{3}H]-8-OH-DPAT (final concentration 1 nM) and 150 μL diluted membranes (10 μg protein per well) prepared in assay buffer (50 mM Tris, pH 7.4, 10 mM $MgSO_4$, 0.5 mM EDTA, 0.1% ascorbic acid) were transferred to polypropylene 96-well microplate using 96-wells pipetting station Rainin Liquidator (MettlerToledo). Serotonin (10 μM) was used to define nonspecific binding. Microplate was covered with a sealing tape, mixed and incubated for 60 min at 27 °C. The reaction was terminated by rapid filtration through GF/C

filter mate presoaked with 0.3% polyethyleneimine for 30 min. Ten rapid washes with 200 μL 50 mM Tris buffer (4 °C, pH 7.4) were performed using automated harvester system Harvester-96 MACH III FM (Tomtec). The filter mates were dried at 37 °C in forced air fan incubator and then solid scintillator MeltiLex was melted on filter mates at 90 °C for 4 min. Radioactivity was counted in MicroBeta2 scintillation counter (PerkinElmer). Data were fitted to a one-site curve-fitting equation with Prism 6 (GraphPad Software) and K_i values were estimated from the Cheng-Prusoff equation.

4.2.4. D_2 receptor binding assay

Radioligand binding was performed using membranes from CHO-K1 cells stably transfected with the human D_2 receptor (LifeTechnologies). All assays were carried out in duplicates. 50 μL working solution of the tested compounds, 50 μL [^{3}H]-methylspiperone (final concentration 1 nM) and 150 μL diluted membranes (5 μg protein per well) prepared in assay buffer (50 mM HEPES, pH 7.4, 50 mM NaCl, 5 mM $MgCl_2$, 0.5 mM EDTA) were transferred to 96-well microplate. Haloperidol (10 μM) was used to define nonspecific binding. Microplate was covered with a sealing tape, mixed and incubated for 60 min at 37 °C. The reaction was terminated by rapid filtration through GF/C filter mate presoaked with 0.5% polyethyleneimine for 30 min. Ten rapid washes with 200 μL 50 mM Tris buffer (4 °C, pH 7.4) were performed using automated harvester system Harvester-96 MACH III FM (Tomtec). The filter mates were dried at 37 °C in forced air fan incubator and then solid scintillator MeltiLex was melted on filter mates at 90 °C for 4 min. Radioactivity was counted in MicroBeta2 scintillation counter (PerkinElmer). Data were fitted to a one-site curve-fitting equation with Prism 6 (GraphPad Software) and K_i values were estimated from the Cheng-Prusoff equation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2020.103662.

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